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Specific Cardiovascular Drugs Utilized in the Critically Ill

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The ability to manipulate the function of the heart and peripheral vasculature is requisite for the management of many critically ill patients. For each clinical situation, a wide scope of cardiovascular agents is available. In this article we review the clinical indications and cardiovascular effects of catecholamines, opioid peptide antagonists, prostaglandin inhibitors, calcium, glucagon, calcium channel blockers, and other agents. We also present possible new indications for "conventional" drugs and discuss future research areas. *Reports; (K7) d*

CATECHOLAMINES

After volume resuscitation is accomplished, catecholamines are the mainstay of treatment for the failing cardiovascular system. The pharmacologic profile of these drugs is reviewed in the following section. The discussion on catecholamines applies to adult patients. The use of catecholamines in children is discussed elsewhere.¹⁵⁰

Epinephrine

Epinephrine-induced actions are mediated by either alpha- or beta-adrenergic receptors, depending on the dose utilized (Table 1). In the dose range of 0.1 to 4.0 $\mu\text{g/kg/min}$, epinephrine's actions are predominately "beta" mediated and include cardiac inotropic and chronotropic effects. The cardiac effects of epinephrine are due to beta₁-adrenergic receptor

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Table 1. Selectivity of Catecholamines for Adrenergic Receptors*

CATECHOLAMINE	α_1	α_2	β_1	β_2	DA**
Epinephrine	+++†	+++	+++	+++	0
Norepinephrine	+++	+++	+++	+	0
Isoproterenol	0	0	+++	+++	0
Dopamine‡	0 to +++	+	++ to +++	++	+++
Dobutamine	0 to +	0	+++	+	0

*From Zaritsky, A., and Chernow, B.: Catecholamines, sympathomimetics. In Chernow, B., and Lake, C. R. (eds.): *The Pharmacologic Approach to the Critically Ill Patient*. Baltimore, Williams and Williams, 1983, with permission.

†+ = Relative degree of stimulation; 0 = no stimulation.

‡Variable, dose-dependent effects. High doses produce predominantly α -adrenergic effects.

**DA = dopaminergic receptor.

stimulation. Epinephrine therapy causes increases in heart rate, left ventricular stroke work index (LVSWI), stroke volume (SV), cardiac output, and systolic blood pressure. Myocardial oxygen consumption also rises owing to the epinephrine-induced increases in LVSWI and systolic blood pressure, both of which increase myocardial work. If a fixed obstruction is present in the coronary bed, coronary blood flow cannot increase.⁵⁸ In this setting, epinephrine therapy may decrease cardiac efficiency (work performed/oxygen consumption).^{78, 133}

Epinephrine stimulates alpha-adrenergic receptors when infused at dosage rates greater than 20 $\mu\text{g}/\text{min}$. Both preload and afterload are increased at these epinephrine dosages, owing to diffuse vasoconstriction. This alpha-mediated nonspecific vasoconstriction predisposes to renal, mucocutaneous, and skeletal muscle ischemia secondary to reduced blood flow to these organs.

At low doses, epinephrine's cardiac effects may produce ectopy and tachycardia because epinephrine increases conduction velocity through the SA and AV nodes, and accelerates ectopic foci. The refractory period of the myocardium is also shortened. Low doses of epinephrine may also cause hypertension and myocardial ischemia. At high doses, epinephrine may produce hypertension, myocardial ischemia, and ischemia of the splanchnic, renal, and mucocutaneous vascular beds, as mentioned earlier. The threshold plasma epinephrine levels at which hemodynamic effects occur remain unclear, especially with low doses of epinephrine.¹⁵

Low dose epinephrine is used for inotropic support (without severe vasoconstriction), for the treatment of bronchoconstriction secondary to asthma, and for reversal of anaphylaxis. Epinephrine may be given via the endotracheal tube when venous access is not available.¹⁶

Norepinephrine

Norepinephrine possesses both alpha- and beta₁-adrenergic effects but has little beta₂-adrenergic effect. The effects of norepinephrine on the heart do not become evident until the infusion rate reaches 2.5 to 5.0 $\mu\text{g}/\text{min}$.¹²² Norepinephrine's positive inotropic actions cause increases in systolic blood pressure, diastolic blood pressure, and mean arterial pressure (MAP). The

pulse pressure widens and (in the nonseptic patient) systemic vascular resistance increases markedly. The increase in MAP leads to a reflex decrease in heart rate, and cardiac output may also decrease.²

Cardiac work load and oxygen demand both rise as a result of increases in preload (increased venous return), afterload (increased systemic vascular resistance), and myocardial contractility (beta₁-adrenergic stimulation). Metabolic autoregulation and a widening of the pressure gradient between MAP and left ventricular end diastolic filling pressure increase coronary artery blood flow in the absence of coronary artery disease.⁷⁸

Norepinephrine has only limited application in the treatment of critically ill patients because of its intense alpha-adrenergic vasoconstricting effects. The intense vasoconstriction may lead to ischemia of the peripheral vascular beds. Boluses of norepinephrine may cause severe hypertension, with resulting myocardial ischemia, myocardial infarction, or cerebral hemorrhage.¹⁴³ In our opinion, norepinephrine is indicated when hypotension is refractory to other vasoconstrictors such as dopamine.

Isoproterenol

The actions of isoproterenol are almost exclusively mediated by beta₂-adrenergic receptors, resulting in potent inotropic and chronotropic effects. Heart rate, dP/dt, and systolic blood pressure increase while left ventricular end diastolic pressure (LVEDP) and diastolic blood pressure fall.⁹² Isoproterenol increases cardiac output, but most of the increased blood flow is delivered to the skeletal muscle bed rather than to the renal and splanchnic beds.

Isoproterenol's positive inotropic and chronotropic effects significantly increase myocardial oxygen consumption. A secondary increase in coronary perfusion occurs⁹²; however, if myocardial ischemia is present, the metabolic requirements of the heart also increase.¹⁰⁵

Isoproterenol causes peripheral vasodilation, owing to its beta₂-adrenergic-mediated effects. The shunting of blood flow to the skeletal muscle bed may decrease MAP and further jeopardize coronary artery perfusion.⁷³ Isoproterenol is thus a poor agent for the treatment of shock.¹⁷

Isoproterenol is useful for treating sinus bradycardia and occasionally for severe asthma.

Dopamine

Dopamine is one of the newer catecholamines utilized for cardiovascular support. Depending on the dosage used, dopamine's actions are mediated by alpha-adrenergic, beta-adrenergic, or dopamine receptors.

When dopamine is infused at rates of 0.5 to 2.0 $\mu\text{g/kg/min}$, it increases renal blood flow, glomerular filtration fraction, and urine output.⁴² These effects are mediated via dopamine receptors in the kidney, renal arterioles, and adrenals. Dopamine may act on the renal tubular cells directly^{43, 60} or indirectly by decreasing aldosterone release.^{45, 144} The result is that sodium excretion increases proportionately more than glomerular filtration rate or renal blood flow.

Dopamine in the dose range of 5 to 10 $\mu\text{g/kg/min}$ has beta-adrenergic effects on the heart. Cardiac contractility and cardiac output increase;

however, there is little change in heart rate, blood pressure, or systemic vascular resistance.^{43, 44} At the higher range of "beta" infusion rates (8 to 12 $\mu\text{g/kg/min}$), dopamine further increases cardiac output with only small rises in heart rate and blood pressure.⁴³

Dopamine exerts alpha-adrenergic effects when the dose exceeds 20 $\mu\text{g/kg/min}$. Diastolic blood pressure, MAP, and systemic vascular resistance are all increased secondary to dopamine-induced vasoconstriction.¹¹⁶ Pulmonary capillary wedge pressure also increases.^{43, 83, 94, 100, 101, 124} The increase in preload leads to an elevation in myocardial wall tension and myocardial oxygen requirements, with pulmonary edema being a potential complication.⁹⁴ Furthermore, alpha-adrenergic-mediated vasoconstriction of the renal artery negates the dopamine receptor-mediated increases in renal blood flow.^{42, 44}

"Low dose" dopamine (0.5 to 2 $\mu\text{g/kg/min}$) is commonly used to increase renal blood flow and urine output. Dopamine at higher doses (more than 5 $\mu\text{g/kg/min}$) is used to increase cardiac output and MAP. Dopamine infusion may cause hypertension, tachycardia, tachyarrhythmias, and myocardial or peripheral ischemia.

Dobutamine

Dobutamine, a synthetic catecholamine, is a selective beta₁-adrenergic agonist with minimal beta₂- or alpha-adrenergic effects (see Table 1).^{44, 123, 137, 142} When dobutamine is infused at 5 to 10 $\mu\text{g/kg/min}$ cardiac output, LVEDP, and LVSWI are all improved. Dobutamine mediates an increase in myocardial contractility with no change in MAP or heart rate.^{40, 44, 90, 91, 124} Dobutamine is utilized in congestive heart failure to decrease pulmonary artery pressure and pulmonary capillary wedge pressure and improve cardiac output and the ejection fraction.^{40, 90, 91, 94} In septic shock, dobutamine exerts its beneficial effects by increasing LVSWI, MAP, and cardiac index.⁸⁴

Dobutamine does not mediate the release of norepinephrine;¹³⁷ it acts directly to increase SA node automaticity and augment AV node and ventricular conduction rates.⁹⁵ Dobutamine does not stimulate dopamine receptors.^{123, 137, 142}

Urinary output may be increased in a patient in shock when dobutamine is infused because of dobutamine-mediated increases in cardiac output, since dobutamine has no direct effect on renal blood flow.⁹¹ In dogs, dobutamine (8 $\mu\text{g/kg/min}$) increases the per cent of cardiac output delivered to the skeletal muscle bed but decreases the per cent of cardiac output provided to the kidneys.^{116, 142}

The most common complication of dobutamine therapy is dysrhythmias; however, they are seen less often with this drug than when dopamine or isoproterenol is used. Because of its selective beta₁-adrenergic effect, dobutamine also causes less tachycardia than isoproterenol while achieving the same inotropic effect.^{85, 137, 142} Other side effects of dobutamine include hypertension, myocardial ischemia, and tachycardia.

Dobutamine is indicated for the treatment of hypodynamic septic shock, cardiogenic shock, or congestive heart failure.

OPIATE ANTAGONISTS

Within the past 6 years, endogenous opioids have been found to play an important role in the pathophysiology of shock caused by sepsis, hemorrhage, and spinal cord trauma. Holaday and Faden initially reported that naloxone, an opiate receptor antagonist, ameliorated the hypotension of experimental hypovolemic²³ and endotoxin shock.⁶⁵ In normal human subjects, low dose naloxone, given intravenously, has no effect on cardiac function.²⁶ The cardiovascular actions of naloxone in shock are mediated by its interaction with opioid receptors.²⁶

Naloxone, in doses as small as 0.1 mg/kg, improves survival in experimental endotoxin shock.¹¹⁵ The cardiovascular effects of naloxone in endotoxin shock include increases in MAP, stroke volume, cardiac output, and cardiac contractility.⁶⁶ There is no naloxone-induced effect on heart rate, systemic vascular resistance, central venous pressure, or pulmonary artery pressure.⁶⁶ Oxygen consumption and serum lactate levels are also unchanged, but oxygen availability increases following administration of naloxone.¹³⁵ These effects of naloxone in endotoxin shock have been observed in cats, dogs, mice, rats, pigs, and monkeys.⁶⁶

Naloxone is beneficial in the treatment of hypovolemic shock. In experimental hemorrhagic shock in rats and dogs, naloxone (without volume replacement) improves cardiac output, MAP, and survival.^{27, 140} The beneficial effects of naloxone in hemorrhagic shock have been confirmed in cats,^{19, 29} rabbits,¹¹⁸ and monkeys.⁴⁹

Thyrotropin-releasing hormone (TRH) is a tripeptide that mediates the release of thyroid-stimulating hormone and prolactin from the pituitary gland. TRH is also a neurotransmitter with a broad range of effects. TRH is an endogenous "physiologic" opiate antagonist that does not affect opiate-induced analgesia^{72, 79} but does reverse other opiate-induced actions such as hypothermia and respiratory depression. TRH, unlike naloxone, elevates blood pressure in control animals^{50, 67} by a mechanism that is not adrenergically mediated.^{5, 74, 140}

TRH reverses hypotension in experimental endotoxin shock by both central and peripheral actions, as evidenced by TRH's reversal of hypotension whether it is given intracerebroventricularly (ICV)⁷⁰ or intravenously.⁶⁷ Adrenal demedullation blocks the cardiovascular effects when TRH is given ICV but not when it is given IV.⁷¹ In experimental endotoxin shock in rats, TRH improves survival⁷⁰ and also elevates systemic vascular resistance (unlike naloxone).¹⁴⁹ Furthermore, naloxone and TRH have additive effects in their reversal of hypotension in endotoxin shock.⁶⁹ Human trials of naloxone and TRH are needed prior to clinical use of these agents.

PROSTAGLANDIN INHIBITORS

The prostaglandins are a diverse group of compounds that are all derived from phospholipids. They are believed to be involved in the etiology of septic, endotoxin, and hemorrhagic shock because plasma prostaglandin levels are elevated in these states.^{33, 35, 37, 38, 82} Further support

for the involvement of endogenous prostaglandins in shock states is evidenced by the fact that cyclo-oxygenase inhibitors ameliorate the altered hemodynamics of experimental shock states.

Ibuprofen is a cyclo-oxygenase inhibitor that enhances myocardial calcium transport¹³⁶ and diminishes platelet and leukocyte aggregation and trapping in the vasculature.³ Ibuprofen improves survival in experimental endotoxin shock when used as a pretreatment in dogs (12.5 to 25 mg/kg),⁸⁰ rats (0.1 to 30 mg/kg),¹⁴⁵ and sheep (10 mg/kg).¹²³ The cardiovascular and pulmonary effects of ibuprofen in shock include increasing MAP and total peripheral resistance,¹³⁶ reversal of pulmonary hypertension,¹²³ and an increasing cardiac index. Ibuprofen also improves abnormal lung mechanics¹²³ and prevents the development of acidosis.⁸⁰

Aspirin pretreatment (15 mg/kg)³³ and indomethacin post-treatment (1.5 to 3.0 mg/kg)^{38, 121} but not indomethacin pretreatment^{36, 146} increase survival in rat endotoxin shock. Indomethacin post-treatment is associated with normalization of cardiac output, heart rate, systemic vascular resistance, and pulmonary artery pressure.^{21, 31} Indomethacin may act directly to block prostaglandin synthesis,⁴⁶ or it may inhibit a "cardiodepressant factor" circulating in the blood.¹¹

Thromboxane synthetase inhibitors, leukotriene antagonists, and prostaglandins themselves are currently being investigated for use in the treatment of shock. The thromboxane synthetase inhibitor OKY 1581 reduces endotoxin-mediated pulmonary hypertension,¹² and another thromboxane synthetase inhibitor, U-63, 557A, prolongs survival in traumatic shock in rats.⁴⁵ Leukotriene antagonists may prove to be beneficial in septic shock, since leukotrienes C₄ and D₄ increase vascular permeability.⁹³ Certain prostaglandins may also be beneficial in endotoxin shock. For example, PGE₁ and PGF_{2α} improve cardiac output and hypotension when used as a pretreatment in canine endotoxin shock.¹¹⁴ As with naloxone, clinical trials of prostaglandin inhibitors are needed.

CALCIUM AND GLUCAGON

Calcium is intimately involved in normal myocardial function. The cardiovascular effects of exogenous calcium include positive inotropy,^{113, 130} diuresis,¹³⁴ and vasodilation.⁷³ Intravenous infusion of calcium causes a transient tachycardia followed by bradycardia.¹¹³ In normocalcemic animals, calcium increases arterial pressure, probably secondary to a calcium-induced increase in stroke work.⁷³ In hypocalcemic animals, calcium increases arterial pressure, stroke volume, and stroke work.¹⁴⁸ Hypocalcemia in humans may lead to cardiac failure that is refractory to digitalis and furosemide but does respond to calcium therapy.¹⁸

Glucagon has both inotropic and chronotropic effects,^{87, 99, 112} which are probably due to its enhancement of calcium flux into myocardial cells¹⁰⁹ and elevation of intracellular cyclic AMP levels.¹³² Glucagon's inotropic effects are independent of adrenergic receptors or catecholamines;^{41, 99, 112} however, its chronotropic effects may be catecholamine mediated.³¹

Glucagon has been used to treat heart failure and cardiogenic shock

Table 2. Relative Effects of Calcium Channel Blocking Agents on Various Cardiovascular Functions*†

	NIFEDIPINE	VERAPAMIL	DILTIAZEM
Negative chronotropic action	1‡	1	½
Negative inotropic action	1	⅓	⅓
Negative dromotropic action	1	½	½
Vasodilator action	1	⅓	⅓

*Ascertained from the addition of equimolar doses of the different Ca⁺⁺ channel blocking agents to isolated tissue preparation.

†From Antman, E. M.: Calcium channel blocking agents in the treatment of cardiovascular disorders. Part II: Hemodynamic and clinical applications. *Ann. Intern. Med.*, 93:886-904, 1980, with permission.

‡Numbers represent relative effect. For example, diltiazem has ½ as much negative chronotropic action as verapamil.

with good results.^{22, 26} It increases myocardial efficiency¹ and predisposes the patient to fewer arrhythmias than would be experienced with beta-adrenergic receptor agonists.²⁴ Glucagon is given as 1 to 5 mg boluses every 20 to 30 minutes or as a continuous infusion (1 to 20 mg/hr).

Glucagon has beneficial effects in experimental septic^{8, 48} and hemorrhagic shock.^{9, 51} In these states, glucagon increases cardiac output, heart rate, and stroke volume while decreasing MAP and peripheral vascular resistance.

CALCIUM CHANNEL BLOCKERS

In the past 10 years, calcium channel blockers have become important drugs in the treatment of critically ill patients. They have important effects on the coronary circulation, the peripheral circulation, myocardial contractility, and the cardiac conduction system.

Calcium channel blockers cause coronary artery dilation and increased coronary blood flow by decreasing coronary vascular resistance.³² Blood flow through collateral vessels in the coronary bed is also increased, which is important in minimizing the size of an ischemic area in the myocardium.^{20, 57, 107, 109, 136}

Calcium channel blockers cause peripheral arterial dilation in many important vessels, including the pulmonary artery,³² the renal artery,^{34, 77} the hepatic artery,⁷⁸ and the splanchnic beds.^{76, 117} The largest increase in blood flow occurs in the femoral artery followed by the coronary, renal, and mesenteric arteries.^{53, 110} The generalized peripheral arterial dilation leads to a fall in systemic vascular resistance.^{96, 139}

Calcium channel blockers have a negative inotropic effect on the heart, the magnitude of which varies with the agent utilized^{108, 119} (Table 2). This causes myocardial oxygen consumption to decline. However, if the calcium channel blocker causes significant peripheral arterial dilation, the negative inotropic effect may be overcome by a reflex tachycardia and positive inotropic effect.^{4, 141} For example, nifedipine causes significant vasodilation,

which activates intense reflex adrenergic effects. Nifedipine's net effect is vasodilation with minimal inotropic effects.¹³¹ Therefore, calcium channel blockers decrease myocardial oxygen demand by negative inotropic effects and increase myocardial oxygen supply by coronary artery dilation.

Calcium channel blockers also affect the cardiac conduction system. Verapamil, the most intensely studied calcium channel blocker, prolongs AV node conduction and increases the refractory period of the AV node, but does not alter intra-atrial conduction time or prolong the QRS or Q-T interval.^{36, 151}

Calcium channel blockers are indicated for use in angina pectoris, Prinzmetal's variant angina, unstable angina pectoris, hypertrophic cardiomyopathy, myocardial infarction, and supraventricular arrhythmias.

ATP-MgCl₂

ATP-MgCl₂ has been demonstrated to improve survival following hemorrhagic shock^{14, 23, 63, 88, 89} in rats and pigs. It is believed that ATP-MgCl₂ treatment reverses a marked depression in reticuloendothelial function that occurs after hemorrhagic shock.¹⁴ ATP-MgCl₂ may mediate its effects on reticuloendothelial function by increasing ATP levels in hepatocytes and Kupffer cells¹³ or by increasing hepatic blood flow.¹⁰⁹

ATP-MgCl₂ improves survival in other conditions such as peritonitis-induced sepsis,⁶¹ severe burns,¹⁴⁵ and postischemic hepatic failure.^{62, 64} In endotoxin shock, ATP-MgCl₂ has a protective effect with improvement of glucose homeostasis.^{30, 39}

Dichloroacetate

Dichloroacetate is a drug that decreases lactic acidosis from many causes, including hypoxia,⁹⁷ epinephrine infusion,^{96, 97} renal disease,¹²⁷ diabetes mellitus,^{128, 129} and exercise.^{102, 130} Dichloroacetate infusion also increases blood pressure, probably secondary to increased myocardial energy metabolism and myocardial contractility.¹²⁷ In experimental myocardial ischemia¹⁰⁴ and lactic acidosis,¹¹¹ dichloroacetate stimulates aerobic oxidative metabolism in the heart, leading to improved myocardial function, which is manifested by an increased cardiac output.

OTHER "CONVENTIONAL" AGENTS

Many commonly used "noncardiac" drugs have cardiovascular effects in normal subjects and in those with endotoxin or septic shock. For example, T₃ may elevate MAP in patients with septic shock.^{39, 103} In endotoxin shock, glucose, insulin, and potassium infused together increase cardiac output, MAP, myocardial contractility, and coronary blood flow.^{9, 10} In primate endotoxin shock, lidocaine elevates MAP and improves survival.³⁵

FUTURE RESEARCH AREAS

New concepts of vascular tone regulation are currently evolving. A new second messenger system called the "phosphatidylinositol/protein

kinase C cascade" has recently been shown to be important in maintaining vascular smooth muscle tone.^{6,7} Modulation of this system may be possible in the future.

Calcium channel activators (such as BAYK 8644) and calcium channel blockers specific for vascular smooth muscle (such as nimodipine) may be used to alter vascular smooth muscle tone.⁴⁷ Neuropeptide tyrosine is a recently discovered neuropeptide that potentiates norepinephrine's effects on smooth muscle.²⁵ Neuropeptide tyrosine agonists and antagonists could alter norepinephrine-induced vascular contraction.

CONCLUSION

In this article we have reviewed the cardiovascular actions of catecholamines, opioid peptide antagonists, prostaglandin inhibitors, calcium, glucagon, calcium channel blockers, and other agents. In treating critically ill patients it is essential to know which drugs are most beneficial in a particular clinical setting. Research into new areas of cell biology will allow more sophisticated manipulation of the cardiovascular system in the future.

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